



**Supplemental Figure 7. Molecular characterization of disseminated cancer cells is required to understand the stage of metastatic progression at which Nkx2-1 and genes associated with the Nkx2-1<sup>neg</sup> state function.**

**A. Progression and selection during metastatic expansion:** Nkx2-1<sup>pos</sup> cancer cells within primary tumors gain the ability to disseminate without down-regulating Nkx2-1. These Nkx2-1<sup>pos</sup> cancer cells can enter secondary sites with the major selection for down-regulation of Nkx2-1 being at the level of metastatic expansion. Note that in this model primary tumors could still progress to an Nkx2-1<sup>neg</sup> state but this is not required for dissemination nor would that necessarily endow the cells with the ability to disseminate.

**B. Progression within the primary tumor with selection at the level of metastatic seeding:** Cancer cells within primary tumors gain the ability to disseminate prior to down-regulating Nkx2-1. Both Nkx2-1<sup>pos</sup> and Nkx2-1<sup>neg</sup> cells disseminate but only Nkx2-1<sup>neg</sup> cells have the ability to seed and subsequently expand into metastases.

**C. Progression within the primary tumor with selection at the level of dissemination:** Progression of the primary tumor to an Nkx2-1<sup>neg</sup> state is a prerequisite before the cancer cells can gain the ability to disseminate. These Nkx2-1<sup>neg</sup> cells gain phenotypes that promote dissemination.

This is not an exhaustive outline of all possible scenarios but represents three distinct models of lung adenocarcinoma metastatic progression that can only be distinguished by the isolation and molecular characterization of DTCs.